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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,134	09/14/2006	Irina Velikyan	PH0334	7198

36335 7590 03/09/2009

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
03/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,134	VELIKYAN ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/09 has been entered.

Claims and Previous Rejections Status

2. Claims 1-16 are pending in the application. Claim 16 was newly added in the amendment filed 1/14/09 and thus the rejections are modified to include claim 16.

3. The rejection of claims 1-15 under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (WO03/059397) in view of the combined disclosures of Yngve (Int. Diss. Abs. **2001**, *62*) and Bottcher et al. (US 5,439,863) and in further view of Maier-Borst et al. (GB 2056471A) is maintained.

4. The provisional rejections of claims 1,3-7 and 15 under 35 U.S.C. 101 as claiming the same invention as that of claims 8-14 of copending Application No. 10/552,206 is maintained.

5. The provisional rejections of claims 1,3-6 and 9-14 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4,8-13 of copending Application No. 11/358,681 is withdrawn.

6. The provisional rejections of claims 1-15 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2,8-15,18, and 19 of copending Application No.10/552,206 and of claims 1-14 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims1-5 and 8-14 of copending Application No. 11/358,681 are maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (WO03/059397) in view of the combined disclosures of Yngve (Int. Diss. Abs. **2001**, *62*) and Bottcher et al. (US 5,439,863) and in further view of Maier-Borst et al. (GB 2056471A).

9. Griffiths et al. (WO03/059397) discloses a radiolabeling method for the preparation of a NOTA or DOTA (containing N hard donor atoms) labeled ^{68}Ga for use in PET (p18, paragraph 1) and the development of a $^{68}Ge/^{68}Ga$ in-house titanium dioxide generator (p7, paragraph 3; p8). The macrocyclic-chelating agent, such as DOTA may be linked to a peptide that can target the site of a disease, thus generating a bifunctional chelating agent comprising a targeting vector which will be site-specific (p9, paragraph 1). The method of producing a radiolabeled gallium complex involves

reacting the solution of a peptide labeled macrocyclic chelate with the ^{68}Ga diluted from the ^{68}Ge/^{68}Ga titanium dioxide generator which can be fitted with an anion-exchange membrane, such as a Q5F cartridge (p12, paragraph 1; p13, paragraph 2; p16, paragraph 2). Griffiths et al. teaches that the advantage of the gallium-68 generator of the disclosure is that gallium-68 is eluted without unwanted over-dilution (p16, first full paragraph) where the prior art teaches of gallium-68 eluted from previous generators is present in extremely dilute solution, typically under one picomole per milliCurie (p4, paragraph 3). Griffiths et al. (WO03/059397) does not disclose a ^{68}Ga-DOTA-oligonucleotide, the synthesis of the ^{68}Ga-DOTA-peptide complex via microwave, or the anion exchanger of the instant claims.

10. Yngve (Int. Diss. Abs. **2001**, *62*) discloses the preparation of a phosphorothiolated ^{68}Ga-DOTA-oligonucleotide and a ^{68}Ga-DOTA-octreotide for use in PET (p12, paragraph 1; p21, last paragraph; p40, paragraph 2). The production of ^{68}Ga is from a generator system via an ion-exchange column (p39, paragraph 3). The labeling of octreotide (a synthetic octapeptide that show high selectivity for the somatostatin receptor) has been widely investigated due to the role of somatostatin for tumor diagnosis and treatment. Radiolabeled octreotides are routinely used for clinical applications.

11. Bottcher et al. (US 5,439,863) discloses the preparation of metal complex salts via microwave irradiation (column 3, line 45). The complexes are prepared from metal ions, such as those of the second and third main group, not excluding gallium and multitoothed chelating ligands that occupy more than one coordination site on the

central metal atom (column 3, lines 55-59; column 4, lines 44-46). The ligands of the disclosure may include those with dioxime (N and O containing), etc. groups (column 5, lines 20-24). The use of microwave as the high-energy input allows for a continuous conversion, single-stage reaction with short reaction time and ease of separation of the formed complexes (column 4, line 19; column 5, lines 66+; column 6, lines 1-5).

12. Maier-Borst et al. (GB 2056471A) discloses the separation of ^{68}Ga for its parent nuclide with water via passing the eluant from a generator column into an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene and washing the anion exchanger with water (p4, lines 44-48).

13. At the time of the invention it would have been obvious to produce a ^{68}Ga-DOTA-oligonucleotide complex, such as that of Yngve for use as a PET tracer via the production of ^{68}Ga from a ^{68}Ge/^{68}Ga titanium dioxide generator as disclosed by Griffiths et al. Griffiths et al. teaches that the titanium dioxide generator produces gallium-68 that is more concentrated (i.e. nanomolar, micromolar) than one picomole per milliCurie of the prior art. It would have been obvious to substitute an anion exchanger, such as that of Maier-Borst et al., which does not require a chelating agent (i.e. EDTA) for separation, for the anion exchanger of Griffiths et al. to separate ^{68}Ga from its parent nuclide. The disadvantage of forming a ^{68}Ga-EDTA complex via addition of a chelating agent (i.e. EDTA) to elute ^{68}Ga from a metal oxide exchanger was known in the prior art and requires the destruction of the ^{68}Ga-EDTA complex before further processing to obtain radiopharmaceutical agents which is both time-consuming and expensive (see Maier-Borst et al. p1, lines 10-16).

14. The microwave synthesis technique for the method of producing metal-chelate complexes was known by Bottcher et al. at the time of the invention. Therefore, it would have been obvious to one skilled in the art to utilize the microwave acceleration technique for a faster and more reproducible preparation of the ^{68}Ga-DOTA-oligonucleotide complex, such as that of Yngve to generate a complex useful in the treatment or diagnosis of tumors with minimal side product formation. Microwave acceleration techniques have been utilized since the 1980's in a number of production methods for radioactive precursors and radiotracers labeled with positron-emitting nuclides. The microwave method is mostly associated with shortened reaction times and encompasses the microwave conditions of the instant claims. Since the microwave technique was known in the art (Bottcher et al.) one would have a reasonable expectation of success for preparing radiotracer via labeling reactions with this improved microwave technique. The disclosures of Griffiths et al. and Bottcher et al. are both drawn to the same utility (i.e. the preparation of metal complexes) and therefore the results would be predictable for a faster and more efficient preparation via microwave.

Response to Arguments

15. Applicant's arguments filed 1/14/09 have been fully considered but they are not persuasive.

16. Applicant asserts that unlike Maier-Borst et al., in the present invention, gallium-68 is eluted from a commercial generator already in ionic form.

17. Maier-Borst et al. teaches that the gallium-68 released by the ion exchanger of the disclosure is in ionic form in high yield (Maier-Borst et al., p1, lines 59-63).

18. Applicant asserts that the present invention discloses a concentration of $^{68}Ga^{3+}$, which is in the picomolar to nanomolar to micromolar range after the elution in an anion exchanger.

19. Griffiths et al. teaches that the titanium dioxide generator produces gallium-68 that is more concentrated (i.e. nanomolar, micromolar) than one picomole per milliCurie of the prior art.

20. Applicant asserts that in the present invention it is possible to reduce the amount of chelating agent in a subsequent complex formation reaction, which considerably increases the specific radioactivity.

21. The method of the instant claims does not provide for the amount/concentration of chelating agent required for reaction with $^{68}Ga^{3+}$. Therefore, the method of the combined disclosures above using the microwave activation of Bottcher et al. for a faster and more reproducible/efficient preparation of the ^{68}Ga-DOTA-oligonucleotide complex of Yngve encompasses the method of the instant claims and is capable increasing the specific radioactivity via the reduction of the amount of chelating agent.

Double Patenting

22. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re*

Ockert, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

23. Claims 1,3-7 and 15 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 8-14 of copending Application No. 10/552,206. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

24. Claims 1,3-7 and 15 are of this application conflict with claims 8-14 of Application No. 10/552,206. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2,8-15,18, and 19 of copending Application No. 10/552,206. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of producing a radiolabeled gallium complex of the instant claims encompasses the method for producing a ^{68}Ga-radiolabeled complex of copending Application No. 10/552,206. Both inventions involve reacting a ^{68}Ga radioisotope with a bifunctional chelating agent comprising a targeting vector (i.e. peptide or oligonucleotide) via microwave. The microwave technique of copending Application No. 10/552,206 encompasses the microwave conditions of the instant claims. The inventions also include the same peptide or oligonucleotide targeting moiety that may be bound to the chelating agent for site-directed localization. The generation of the ^{68}Ga radioisotope of both applications involves eluting the ^{68}Ga from a ^{68}Ge/^{68}Ga titanium dioxide generator followed by purification of the ^{68}Ga eluate via a strong anion exchanger comprising HCO_3^- counterions. Therefore, the resulting radiolabeled gallium complex of the instant claims is obviously generated via the synthesis and isolated and would encompass that radiolabeled gallium complex of the copending application.

26. This is a provisional obviousness-type double patenting rejection.

27. Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 8-13 of copending Application No. 11/358,681. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of producing a radiolabeled gallium complex of the of the instant claims encompasses the method for labeling synthesis of radiolabeled gallium complex of copending Application No. 11/358,681 since the method steps are identical. Both inventions involve reacting a ^{68}Ga radioisotope with a bifunctional chelating agent comprising a peptide via microwave, using the exact same microwave conditions. The inventions also include a targeting moiety that may be bound to the chelating agent for site-directed localization. The generation of the ^{68}Ga radioisotope of both applications involves eluting the ^{68}Ga from a $^{68}Ge/^{68}Ga$ titanium dioxide generator followed by purification of the ^{68}Ga eluate via a strong anion exchanger comprising HCO_3^- counterions. Therefore, the resulting radiolabeled gallium complex of the instant claims is obviously generated via the synthesis and isolated and would encompass that radiolabeled gallium complex of the copending application.

28. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618